REMARKS

I. Status of the Claims

Claims 1-3, 11-29, 57, 58, 66, 69, 71, 81 and 84-88 are pending in the application. Claims 1-3, 11-29, 57, 58, 66, 69, 71, 81 and 84-88 stand rejected under 35 U.S.C. §112, first paragraph. Claims 1, 2, 14, 15, 22, 23, 27, 57, 58 and 87 are rejected under 35 U.S.C. §103 over Shriver *et al.*

II. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1-3, 11-29, 57, 58, 66, 69, 71, 81 and 84-88 are rejected for alleged lack enablement. More specifically, though the examiner acknowledges that the claims are enabled for use of the RPL14 probe to predict NSCLC, the claims are not considered enabling for prediction of all cancers, or of other aspects of cancer disease such as metastasis, progression or relapse. Applicants traverse.

Attached to this response is an Information Disclosure Statement that includes a number of references that demonstrate, generally, that the 3p21 chromosomal region is involved with a variety of cancers, not simply NSCLC:

- Fan & Rizkalla (2003) - 3p21 involvement in follicular lymphoma and diffuse large B-cell lymphomas
- Chung *et al.* (2000) – 3p21 involvement in cervical intraepithlial neoplasia
- Alimov *et al.* (2000) – 3p21 involvement in renal cell carcinoma
- Junker *et al.* (2003) – 3p21 involvement in renal cell carcinoma
- Siebert *et al.* (1998) – 3p21 involvement in renal cell carcinoma

- Dobler *et al.* (1999) – 3p21 involvement in squamous cell carcinoma, Bowen carinomas and metastatic melanomas

Though admittedly indirect with respect to evidencing the connection with RPL14, this evidence is sufficient, when taken with the information contained in the instant specification to support a broader application of the claimed invention.

In addition, with respect to 10q22, applicants submit that this region also plays a role in multiple cancer types:

- Clark *et al.* (2003) – 10q22 involvement in prostate cancer
- Bissola *et al.* (2002) – 10q22 involvement in oligogastrocytomas
- Fawole *et al.* (2002) – 10q22 involvement in sporadic colorectal adenocarcinoma
- Frayling *et al.* (1997) – 10q22 involvement in colorectal cancer

The other issue relates to enablement of predicting metastasis, progression and relapse. Applicants traverse the rejection, but have canceled those claims (57 *et seq.*, 69 *et seq.*, and 87 *et seq.*) in the interest of advancing the prosecution.

Reconsideration and withdrawal of the rejection is respectfully requested.

III. Rejection Under 35 U.S.C. §103

Claims 1, 2, 14, 15, 22, 23, 27, 57, 58 and 87 are rejected under 35 U.S.C. §103 over Shriver *et al.* Specifically, the examiner argues that Shriver teaches that the 3p region is consistently deleted in cancers, and that the RPL14 gene, which lies in this region, is deleted in a high percentage of lung cancers. Finally, Shriver is said to state that "RPL14 is an important

event in lung carcinogenesis ...." Applicants traverse, and will address the rejection as it applies to each independent claim.

Claim 1. Claim 1 is drawn to a method of identifying a subject at risk of developing lung cancer. The examiner has argued that, though Shriver does not teach assessing risk, the existence of a difference between RPL14 LOH seen in the tissues of cancerous and non-cancerous individuals would render this claim obvious.

Applicants once again traverse. The existence of RPL14 deletions in a cancer patient does not necessarily mean that the existence of RPL14 deletions in "normal" individuals put those individuals at risk of developing cancer. The predictive ability of RPL14 only comes from applicants' studies, and it is pure hindsight on the part of the examiner to now impute such from Shriver alone.

Nonetheless, in the interest of advancing the prosecution, applicants have amended claim 1 to recite a combined analysis, looking at LOH in both RPL14 and the 10q22 region. The attached data clearly indicate that the combination of these two markers provides a much more robust prediction of cancer suscpetibility. As such, amended claim 1 clearly is both enabled and non-obvious. Reconsideration and withdrawal of the rejection of claim 1, and claims dependent thereon, is respectfully requested.

Claim 57. Claim 57 is drawn to a method for predicting the progression or metastasis of non-small cell lung and other carcinoma in a subject having said non-small cell lung carcinoma. Shriver is absolutely silent on these points. And unlike the discussion provided with regard to "predicting susceptibility," the examiner has not even mentioned progression or metastasis in the discussion of obviousness. Thus, on its face, the rejection is improper.

Notably, the examiner has seen fit to take the instant specification to task as lacking evidence that this can be accomplished, which applicants have now rebutted. However, the very same argument can and should be made against Shriver, which does not even mention progression or metastasis. Thus, even acknowledging that the rejection is based on obviousness, it fails to satisfy the required elements of a *prima facie* case, namely, a teaching of each element of the rejected claim, as well as likelihood of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991).

However, in the interest of advancing the prosecution, applicants have canceled claim 57, and claims dependnent thereon.

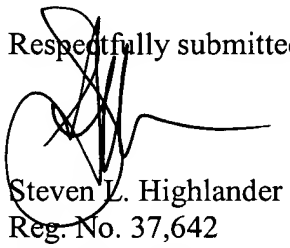
Claim 87. Claim 87 is drawn to a method of identifying an individual to be segregated from a high risk lung cancer environment. The examiner has not attempted to argue that Shriver teaches or suggests this claim, but implies that it is somehow "obvious" in view of Shriver's alleged teaching that LOH for RPL14 is "an important event in lung and oral carcinogenesis." Simply put, this argument is insufficient. As discussed above, the controlling case law requires that a *prima facie* rejection provide a teaching of each element of the claims. Here, even if one were to assume that LOH for RPL14 was predictive of susceptibility, it does ***not*** necessarily indicate that there would be any value to segregating an individual from environmental influences. Thus, in light of *Vaeck*, applicants submit that the rejection is improper as a matter of law.

However, in the interest of advancing the prosecution, applicants have canceled claim 87, and claims dependnent thereon.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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AMENDMENTS

Listing of Claims

The following listing of claims replaces all previous listings or version thereof:

1. (Presently amended) A method for identifying a subject at risk for the development of lung cancer comprising:

(a) obtaining a test sample from a subject;
(b) providing an RPL14 gene probe and a 10q22 DNA gene probe;
(c) contacting said ~~probe~~probes with said test sample; and
(d) analyzing DNA from said test sample for loss of heterozygosity in RPL14 and 10q22,

whereby loss of RPL14 and 10q22 ~~heterozyosity~~ heterozygosity indicates risk for the development of lung cancer.

2. (Previously presented) The method of claim 1, wherein said test sample comprises a surgical or biopsy specimen, a paraffin embedded tissue, a frozen tissue imprint, a sputum, esophageal brush, a fine needle aspiration, a buccal smear or a bronchial lavage.

3. (Previously presented) The method of claim 1, further comprising providing a GC20 gene probe and performing steps (c) and (d) with said GC20 gene probe.

4-10. (Previously canceled)

11. (Original) The method of claim 1, wherein said subject is a smoker.

12. (Original) The method of claim 1, wherein said subject is a former smoker.

13. (Original) The method of claim 1, wherein said subject is a non-smoker.

14. (Original) The method of claim 1, wherein said test sample comes from said subject who has not previously been diagnosed with cancer.

15. (Original) The method of claim 1, wherein said probe is labeled with a fluorophore.

16. (Original) The method of claim 1, wherein said probe is labeled with digoxigenin.

17. (Original) The method of claim 1, wherein said probe size is between 1000 and 2000 base pairs.

18. (Original) The method in claim 1, further comprising a spiral CT-scan.

19. (Previously presented) The method of claim 1, further comprising administering to said subject chemopreventive drugs, nutritional supplements, chemotherapeutic drugs or biological modifying response drugs.

20. (Original) The method of claim 1, wherein said method is used to identify subjects who need an intensive follow-up protocol.

21. (Previously presented) The method of claim 1, wherein said probe is used to identify subjects who are suitable for novel investigational therapeutic approaches.

22. (Original) The method of claim 1, wherein a control probe is used.

23. (Original) The method of claim 22, wherein said control probe is labeled with a fluorophore.

24. (Original) The method of claim 23, wherein said control probe is labeled with spectrum orange.

25. (Original) The method of claim 22, wherein said control probe is a chromosome 3 stable marker.

26. (Original) The method of claim 25, wherein said control probe is Centromere 3 (CEP 3).

27. (Original) The method of claim 1, wherein analyzing comprises using FISH.

28. (Previously presented) The method of claim 1, wherein said probe is used as a biomarker for the early detection of early neoplastic events or cancer.

29. (Canceled) The method of claim 1, further comprising providing a 10q22 DNA gene probe and performing steps (c) and (d) with said 10q22 gene probe.

30-56. (Previously canceled)

57. (Canceled) A method for predicting the progression or metastasis of non-small cell lung carcinoma and other carcinoma in a subject having said non-small cell lung carcinoma comprising:

(a) obtaining a test sample from a subject;
(b) providing an RPL14 gene probe;
(c) contacting said probe with said test sample; and
(d) analyzing DNA from said test sample for loss of heterozygosity in RPL14,

wherein loss of RPL14 heterozygosity predicts progression or metastasis of said non-small cell lung carcinoma.

58. (Canceled) The method of claim 57, further comprising providing a GC20 gene probe and performing steps (c) and (d) with said GC20 gene probe.

59-65. (Previously canceled)

66. (Canceled) The method of claim 57, further comprising providing a 10q22 DNA probe and performing steps (c) and (d) with said 10q22 gene probe.

67-68. (Previously canceled)

69. (Canceled) A method of predicting lung cancer relapse [or development of a new primary lung cancer in a subject] comprising determining loss of heterozygosity in the RPL14 gene and a 10q22 gene in cells of bronchial tissue adjacent to tumor tissue from said subject, wherein loss of RPL14 and 10q22 heterozygosity in said adjacent tissue predicts lung cancer relapse[or development of lung cancer].

70. (Previously canceled)

71. (Canceled) The method of claim 70, wherein said cancer is non-small cell lung carcinoma.

72-80. (Previously canceled)

81. (Canceled) The method of claim 69, further comprising providing a GC20 gene probe and determining loss of heterozygosity in the GC20 gene in cells of bronchial tissue adjacent to tumor tissue from said subject.

82-83. (Previously canceled)

84. (Canceled) The method of claim 69, further comprising providing a 10q22 DNA probe and determining loss of heterozygosity in the 10q22 region in cells of bronchial tissue adjacent to tumor tissue from said subject.

85. (Canceled) The method of claim 69, wherein said test sample comes from the same or contralateral lung.

86. (Canceled) The method of claim 69, wherein said test sample comes from nontumorous bronchial cells.

87. (Canceled) A method of identifying an individual to be segregated from a high risk lung cancer environment comprising:

(a) obtaining a test sample from a subject;
(b) providing an RPL14 gene probe
(c) contacting said probe with said test sample; and
(d) analyzing DNA from said test sample for loss of heterozygosity in RPL14,

whereby loss of RPL14 heteroygosity identifies an individual who is highly susceptible to the development of lung cancer and who should not be exposed to a high risk environment.

88. (Canceled) The method of claim 87, further comprising providing a 10q22, GC20 or PTEN/MMAC1 gene probe and performing steps (c) and (d) with said 10q22, GC20 or PTEN/MMAC1 gene probe.